Treatment effect of switching from intravenous to subcutaneous C1-inhibitor for prevention of hereditary angioedema attacks: COMPACT subgroup findings

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Clinical Implications

- This subgroup analysis of COMPACT trial data suggests that patients with hereditary angioedema using intravenous human C1-inhibitor as routine prophylaxis can derive a clinically meaningful benefit when switched to prophylaxis with subcutaneous human C1-inhibitor, observable as a further reduction in hereditary angioedema attacks.

TO THE EDITOR:

Hereditary angioedema (HAE) is a rare, debilitating, and potentially life-threatening condition typically resulting from deficiency (type 1 HAE) or dysfunction (type 2 HAE) of the C1-inhibitor (C1-INH) protein.[1] International HAE management guidelines recommend that all patients be evaluated for long-term (routine) prophylaxis and that human, plasma-derived C1-INH has been cited as a first-line option.[2] Intravenous (IV) human C1-INH (C1-INH[IV]; Cinryze, Shire), Food and Drug Administration (FDA) approved in 2008,[3] was the first C1-INH product specifically indicated for routine prophylaxis and represented a major advancement in HAE management. However, its use entails an ongoing need for venous access and possibility of related complications. In addition, breakthrough attacks are common at the initial FDA-approved dose, and only a minority of patients are completely attack free.[4-6]

A volume-reduced formulation of human C1-INH for subcutaneous (SC) administration (C1-INH[SC]; HAEGARDA, CSL Behring)[7] was FDA approved in June 2017 for routine prevention of HAE attacks. Twice-weekly administration of C1-INH(SC) significantly reduced HAE attack rate and improved quality-of-life versus placebo in the phase 3 COMPACT trial.[8,9] Although the comparative prophylactic effectiveness of C1-INH(SC) and C1-INH(IV) is of clinical interest, head-to-head data are not available. Thus, an exploratory analysis was performed on a prespecified subgroup of COMPACT study participants who were using C1-INH(IV) for routine prophylaxis before the study; prestudy HAE attack rates while using C1-INH(IV) prophylaxis were compared with on-study attack rates while using C1-INH(SC) prophylaxis.

Detailed methods and primary findings of the COMPACT study have been reported elsewhere.[8] Briefly, the study included a screening period (up to 4 weeks) and a prophylaxis-free run-in period (up to 8 weeks) during which attacks could be treated with rescue HAE therapy, after which subjects were randomized to crossover treatment with either C1-INH(SC) 40 or 60 IU/kg administered twice weekly for 16 weeks, preceded or followed by twice-weekly placebo for 16 weeks. The initial study protocol allowed the use of C1-INH(IV) as prophylaxis within 3 months before screening; this was later amended to preclude such patients because of institutional review board concerns over potentially increased attack frequencies when C1-INH(IV) prophylaxis was withdrawn. Eligible participants were individuals $\geq$12 years of age with type 1 or 2 HAE, with a history of $\geq$4 HAE attacks over any consecutive 2-month period before the use of prophylactic therapy.

The subgroup for this analysis included 21 patients who entered the COMPACT study after using C1-INH(IV) at variable doses for routine prophylaxis of HAE attacks before screening; 13 patients previously used C1-INH(IV) prophylaxis at or above the approved dose and/or frequency of 1000 IU every 3 to 4 days,[3] whereas 8 patients were using regimens involving lower doses and/or frequency than recommended (Table I). The mean (SD) age was 46.3 (18.2) years, and 71% (n = 15) were female. Attack data while using C1-INH(IV) in the 3 months before screening were obtained from patients' medical charts. During the study, investigators recorded attack information in electronic case report forms based on patients' daily electronic diaries (eDiaries). Patients recorded any HAE symptoms (regardless of the need for treatment) in the eDiaries. Eight patients were randomized to a C1-INH(SC) 40 IU/kg sequence and 13 patients were randomized to a C1-INH(SC) 60 IU/kg sequence.

The mean (standard deviation) time-normalized number of HAE attacks (HAE attack rate per month) was determined before screening and during study treatment. The HAE attack rate per month per subject was calculated by dividing the total number of HAE attacks during the period of interest by the number of days of the period, and then multiplying the resulting number of attacks per day by 30.4375 to yield the number of attacks per month. The percentage reduction in monthly HAE attack rate for C1-INH(SC) versus C1-INH(IV) was calculated as follows: 100 $\times$ (1 $-$ [time-normalized number of HAE attacks during treatment with C1-INH(SC)/time-normalized number of HAE attacks prestudy]).

The time-normalized number of HAE attacks (primary endpoint in the COMPACT study) was lower during the on-study use of C1-INH(SC) prophylaxis than during the prestudy use of C1-INH(IV) prophylaxis (mean, 1.2 vs 2.7 attacks/month; median, 0.6 vs 2.0 attacks/month) (Table II). There was a 52.1% mean reduction (73.6% median reduction) in HAE attack rate from the prestudy use of C1-INH(IV) for routine prophylaxis to the on-study use of C1-INH(SC) for routine prevention. Findings were similar for the 40 and 60 IU/kg dose groups individually.

TABLE I. Individual subject data

Prior C1-INH(IV) prophylaxis by subject	Prior C1-INH(IV) dose	C1-INH(SC) dose (IU/kg)	Time-normalized number of HAE attacks (number/mo)	
			Prestudy	C1-INH(SC)40 or 60 IU/kg BIW
Cinryze				
1	1000 IU BIW	40	3.67	1.74
2	1500 IU Q3D	40	11.00	1.45
3	1000 IU BIW	40	3.00	1.16
4	1000 IU BIW	40	2.00	0.00
5	500 IU TIW*	40	1.33	0.29
6	1000 IU BIW	40	0.00	0.00
7	1000 IU BIW	60	1.67	0.00
8	1500 IU BIW	60	1.33	0.00
9	1000 IU QW*	60	1.67	1.15
10	1500 IU Q3D	60	1.33	0.60
11	1000 IU QW*	60	1.67	0.70
12	500 IU BIW*	60	2.00	0.62
13	1000 IU BIW	60	8.00	0.29
14	1000 IU BIW	60	1.67	–
15	1000 IU BIW	60	2.00	0.00
Berinert				
16	1000 IU Q5D*	40	0.00	6.09
17	2000 IU BIW	40	2.33	4.35
18	1000 IU Q4D	60	0.67	1.48
19	2000 IU QW*	60	4.67	0.61
20	500 IU BIW*	60	3.00	0.64
Not specified				
21	1000 IU QW*	40	2.67	2.90
Total				
Mean (SD)			2.65 (2.57)	1.20 (1.58)
Min, Max			0.00, 11.00	0.00, 6.09
Median			2.00	0.63

BIW, Twice weekly; *C1-INH(IV)*, intravenous human C1-inhibitor; *C1-INH(SC)*, subcutaneous human C1-inhibitor; *HAE*, hereditary angioedema; *Q3D/Q4D/Q5D*, every 3/4/5 d; *QW*, once weekly; *SD*, standard deviation; *TIW*, 3 times weekly.
*C1-INH(IV) use at doses lower and/or less frequent than recommended (1000 IU every 3-4 d).

TABLE II. Monthly HAE attack rate by study phase and percentage reduction in attack rate

Study phase	Time-normalized number of HAE attacks/month by the treatment group		
	All subjects N = 21*	C1-INH(SC) 40 IU/kg n = 8	C1-INH(SC) 60 IU/kg n = 12
C1-INH(IV) (prestudy)			
Mean ± SD (95% CI)	2.7 ± 2.6 (1.5, 3.8)	2.9 ± 3.5 (−0.02, 5.9)	2.6 ± 2.0 (1.3, 3.8)
Median (lower, upper quartile)	2.0 (1.3, 3.0)	2.2 (0.7, 3.3)	1.8 (1.5, 2.8)
C1-INH(SC)*			
Mean ± SD (95% CI)	1.2 ± 1.6 (0.5, 1.9)	1.9 ± 2.2 (0.04, 3.7)	0.7 ± 0.8 (0.2, 1.3)
Median (lower, upper quartile)	0.6 (0.1, 1.5)	1.3 (0.1, 3.0)	0.6 (0.1, 0.9)
Percentage reduction in attack rate, C1-INH(SC) on study vs C1-INH (IV) prestudy			
Mean ± SD (95% CI)	52.1 ± 63.6 (20.4, 83.7)	48.8 ± 68.4 (−23.0, 120.5)	53.7 ± 64.2 (12.9, 94.6)
Median (lower, upper quartile)	73.6 (52.6, 96.4)	69.8 (52.6, 86.8)	73.8 (43.2, 98.2)

C1-INH(IV), intravenous human C1-inhibitor; *C1-INH(SC)*, subcutaneous human C1-inhibitor; *CI*, confidence interval; *HAE*, hereditary angioedema; *SD*, standard deviation.
*N = 20 while using C1-INH(SC); 1 subject in the Placebo → C1-INH(SC) sequence discontinued before the C1-INH(SC) period.

In the absence of prospective head-to-head comparisons of C1-INH(IV) and C1-INH(SC), this *post hoc* analysis of COMPACT data provides the first evidence of the relative effectiveness of C1-INH(SC) compared with the recent use of C1-INH(IV). These findings suggest that patients on C1-INH(IV) prophylaxis may experience a clinically meaningful reduction of HAE attacks after switching to C1-INH(SC). On average, attack rates during the C1-INH(SC) use were reduced by about half compared with prestudy C1-INH(IV) prophylaxis; the median reduction of attacks per month was almost 74%.

This analysis has several limitations including a small sample size and some dosing disparities. However, the previous use of C1-INH(IV) reflected real-world, nonstandardized dosing that varied greatly and in some cases was below approved dosing recommendations (Table I).[3] Although it could be assumed that prestudy, real-world treatment was individualized for optimum efficacy because C1-INH(IV) prescribing recommendations allow for doses up to 2500 IU twice weekly,[3] there was no way to confirm such dose/administration frequency optimization for each patient. In this analysis, more than one-third of patients (n = 8) used C1-INH(SC) at a dose of 40 IU/kg during the COMPACT study, which is lower than the approved dose of 60 IU/kg[7]; thus the true treatment difference after switching to approved dosing with C1-INH(SC) (60 IU/kg) may be underestimated by these data. Another limitation is the possibility of patient selection bias, in that patients well controlled on C1-INH(IV) prophylaxis may have been less likely to enroll in the COMPACT study. Finally, the methodology for identifying HAE attacks during the prestudy period was not systematic but based on medical chart entries and patients' histories, thus, not as methodical as the systematic recording of attacks during the COMPACT study treatment phases.

In summary, within the limitations of this subgroup analysis, we conclude that patients previously using C1-INH(IV) at various doses as routine prophylaxis can experience a substantial and clinically meaningful reduction in HAE attack rate when switching to C1-INH(SC). Additional clinical experience and further studies will be needed to confirm these observations.

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